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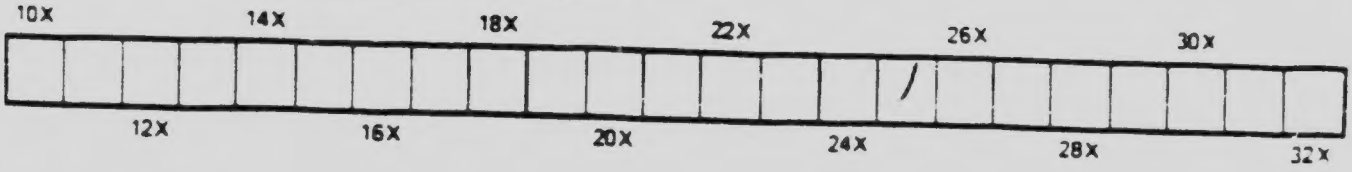

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No. 18: VASCULAR CHANGES PRODUCED BY ADRENALIN IN VERTEBRATES, BY FRANK A. HARTMAN, LESLIE G. KILBORN and ROSS S. LANG

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Vascular Changes Produced by Adrenalin in Vertebrates

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VASCULAR CHANGES PRODUCED BY ADRENALIN IN VERTEBRATES

Frank A. Hartman, Leslie G. Kilborn and Ross S. Lang.

(From the Laboratory of Physiology, University of Toronto.)

The majority of physiologists still teach that adrenalin is essentially constrictor in its effect upon the blood vessels, ignoring the fact that doses which are probably physiological in their magnitude cause dilatation in a large proportion of vessels. These teachings are founded upon the older experiments in which massive doses of the hormone were used. Such amounts of adrenalin are probably never secreted by the adrenal glands (1, 2, 3). Although in the last few years it has been conclusively proven that small quantities of adrenalin cause vasodilatation and a fall in blood pressure as a result (4, 5, 6, 10) the fact is still ignored. This situation may be easily explained, for, among the common laboratory mammals some give evidence of vasodilatation while others consistently fail to do so. These animals which have been found to give positive proof of dilatation belong to the carnivores, while those that do not belong to the rodents. In face of the experimental facts it was as easy to believe the response of cats and dogs exceptional, as that the effect in rabbits was different from that in other animals. In view of this disagreement, it was perfectly natural to assume that the action of adrenalin in cats and dogs was unusual, since it did not conform to other beliefs such as the absence of vasodilator fibers in the sympathetic nervous system.

This research was undertaken with the object of determining whether the dilator action of adrenalin was confined to the carnivores. It was conceivable that other groups might give a similar action, although none were known to do so; accordingly a survey was made of all the groups available. The results have been sufficient to remove all doubt as to the general occurrence of vasodilatation from adrenalin.

A brief sketch of our present knowledge concerning this dilatation is needed as a foundation for this research. The nature of the mechanism on which adrenalin acts was worked out largely by experiments upon cats and dogs. Those experiments have proven that a differential effect is produced—dilatation in skeletal muscle (5, 6) and intestine, (large doses)—constriction in skin (6), intestine (small doses), kidney (8, 10), bone (16), thyroid (15) and spleen (7, 10). With small doses, the vessels in skeletal muscle more than counteract the constriction in the skin and abdominal viscera, so that a fall in blood pressure results. When the amount of adrenalin is sufficiently large, the constriction of skin and visceral vessels (excepting intestine) becomes great enough to more than compensate for the dilatation in skeletal muscle, thus producing a rise in blood pressure.

The dilatation produced by adrenalin has been shown to be brought about by dilator mechanisms located in the sympathetic and dorsal root ganglia (12) as well as in a "terminal" receptive substance which has been called the myoneural junction (13, 14). The latter, a counterpart of the constrictor myoneural junction, is assumed to be associated with dilator fibers.

METHODS

The methods employed in this research were those already described in work from this laboratory (10, 11, 12).

All animals, unless otherwise stated, were anaesthetized with ether. Blood pressure was taken from the carotid artery, except in the fowl, in which case the sciatic artery was used. Injections were made into the jugular vein.

Solutions of adrenalin chloride were made up by diluting the 1:1,000 preparation of Parke, Davis & Co. Volume changes were registered by means of Brodie's bellows. The plethysmograph for the limb was either of the type which enclosed the paw, or else like a cuff, so that the paw might be excluded (13). It was necessary to use artificial respiration in the fowl when the abdomen was opened.

RESULTS

Reptilia (Chelydra)

A snapping turtle (5.3 kgm.) was employed as representative of the reptiles. Doses of adrenalin as small as 0.2 c.c., 1:1,000,000 were tried with no effect upon the blood pressure. Even 0.5 c.c., 1:100,000 had no effect. 1.0 c.c., of the latter concentration caused a rise from 46 mm. to 50 mm. 0.4 c.c. 1:10,000 caused a change from 44 to 54 mm. 1.0 c.c. of the same solution produced about the same effect. Indeed it was found that with large doses, sensitiveness to adrenalin was soon lost. 0.5 c.c., 1:1,000 following the above, increased the pressure only 6 mm. from 51 mm. Repetition of this had no effect, nor did twice the dose. Two months later, the blood pressure and intestinal effects were studied in the same animal. The blood pressure responses were similar. The in-

testine always gave constriction when there was any effect. This was observed with doses ranging from 0.5 c.c., 1:100,000 to 3.0 c.c., 1:10,000. After the latter dose, 1.0 c.c., 1:1,000 produced no intestinal change.

Although only tentative conclusions can be drawn from a single animal, they are at least valuable when considered in connection with other vertebrates low in the scale. We have found that the vascular system of the turtle is not very sensitive to adrenalin and that there is evidence of only a constrictor mechanism. The failure to obtain a fall in blood pressure or a dilatation of the intestine indicate an absence of the dilator mechanisms.

Aves (Gallus)

The fowl serves as an example of the warm blooded vertebrate other than the mammal. It is much more sensitive to adrenalin than are the cold-blooded vertebrates. Moreover it does not easily lose its power to respond to this hormone, even after numerous doses.

Constriction is the only effect produced by adrenalin in the fowl. Both the limb (Fig. 1) and the intes-

FIG. 1
Effect of 0.5 c.c., 1:100,000 adrenalin upon the limb in the fowl. 1.0 kgm. (Reduced ⅝.)

tine (Fig. 2) respond in this way. From a study of

FIG. 2
Prolonged constriction of the intestine in the fowl. (0.92 kgm.) Produced by 0.5 c.c., 1:10,000 adrenalin. (Reduced ⅔).

seven animals no evidence of the existence of the adrenalin vasodilator mechanisms (Table 1) has been found.

TABLE I.
RESPONSE TO ADRENALIN IN THE FOWL

Weight in kgm.	Dose	Blood pressure change in mm. of mercury	Limb	Intestine
1.1	0.2 cc 1:1,000,000		Slight constriction	
	0.5 cc 1:100,000	109-138	Constriction	
	1.0 cc "	114-182	Marked constriction	
1.0	0.1 cc 1:100,000	118-130	Constriction	
	0.5 cc "	106-134	Marked constriction	
0.92	0.2 cc "	65- 79	Constriction	Constriction
	0.5 cc "	95-175		Marked constriction
0.85	0.2 cc 1:1,000,000	52- 54	Constriction	
	0.5 cc 1:100,000	55- 65	Marked constriction	Constriction
	1.0 cc "	80-119		Constriction
0.95	0.5 cc 1:100,000			Constriction
	0.5 cc 1:10,000			Very marked constriction

MAMMALIA

Marsupialia (Didelphys)

A single opossum about two-thirds grown (weight 1.3 kgm.) was used in this research. A fall in blood

pressure (Fig. 3) was easily obtained from adrenalin.

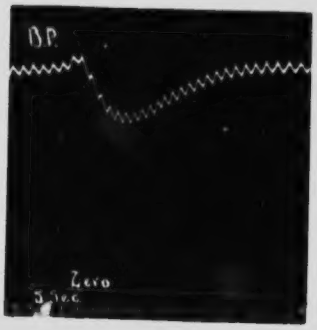

FIG. 3
Blood pressure fall in the opossum produced by 0.2 c.c. 1:100,000 adrenalin (Reduced ⅓.)

This was usually preceded by a brief rise. With larger doses pure pressor effects resulted.

Although the limb included in the plethysmograph possessed a smaller proportion of muscle than that in most mammals it gave active dilatation (Fig. 4) ex-

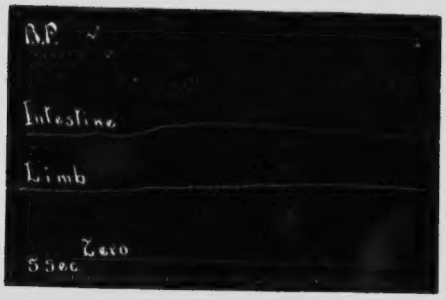

FIG. 4
Dilatation of limb and intestine in the opossum caused by a depressor dose of adrenalin, 0.2 c.c., 1:10,000. (Reduced ⅓.)

cept when large doses were used. The intestine dilated actively in response to adrenalin (Fig. 5), the dilatation becoming very marked with large doses (Table II).

FIG. 5
Marked dilatation of the intestine in the opossum resulting from the injection of a pressor dose of adrenalin 0.5 c.c., 1:10,000 (Reduced ⅓.)

TABLE II.
RESPONSE OF THE OPOSSUM TO ADRENALIN

Dose	Blood pressure change in mm. of mercury	Response of limb	Response of Intestine
0.05 cc 1:100,000	140-142-136		Dilatation
0.1 cc "	138-144-128		Dilatation
0.2 cc "	144-151-135	Slight constriction	Dilatation
0.5 cc "	118-125-106	Dilatation	Constriction and dilatation
0.5 cc 1:10,000	123-180	Small dilatation	Marked dilatation
1.0 cc "	98-215	Small dilatation	Marked dilatation

We may conclude then that the opossum and probably all marsupials possess adrenalin vasodilator mechanisms similar to those in the cat and dog.

UNGULATA

Perissodactyla (Equus)

Unfortunately the horse which we used was in such poor condition that it cannot be considered typical. It was anaesthetized with chloroform, and 1:1000 adrenalin was injected in every instance. In no case was there a fall in blood pressure. 5.0 c.c., adrenalin changed the pressure from 114 mm. to 162 mm.

10.0 c.c. increased the pressure from 80 to 260 mm.

Attempts to produce dilatation of the intestine were successful when 25.0 c.c. was injected, there being a strong constriction followed by a dilatation. 20.0 c.c. produced constriction only.

Intestinal dilatation was the only indication of the presence of an adrenalin vasodilator mechanism in the horse.

Artiodactyla (Capra)

In view of the unsatisfactory condition of the horse, it was imperative that another animal belonging to the ungulates be tried. An experiment with a goat (weight 13.0 kgm.) removed all doubt as to the existence of adrenalin vasodilator mechanisms in this order. A depressor effect (Fig. 6) as well as

FIG. 6
Fall in blood pressure from 0.4 c.c. 1:100,000 adrenalin in the goat, 13.0 kgm. (Reduced ½.)

active dilatation of the limb (Fig. 7) could be obtained from the injection of small amounts of adrenalin. However nothing but constriction in the intestine (Fig. 8) resulted from even large doses of adrenalin until perfusion was attempted. A loop of intestine, with nerves intact, but shut off from the general circulation and perfused with oxygenated Ringer's solution gave pronounced dilatation both when

FIG. 7
Dilatation of the limb and constriction of the intestine produced by 0.5 c.c., 1:100,000 adrenalin in the goat. (Reduced ⅓.)

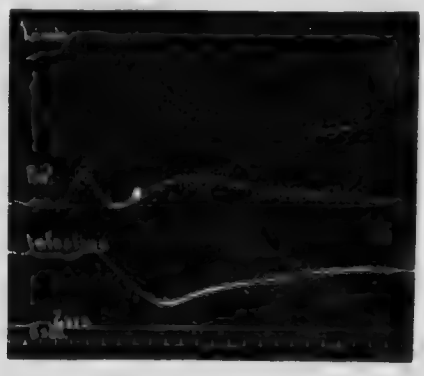

FIG. 8
Constriction in the limb and intestine caused by 1.0 c.c., 1:10,000 adrenalin, goat. (Reduced ⅓.)

TABLE III.
RESPONSE OF THE GOAT TO ADRENALIN

Dose	Blood pressure, mm. of mercury	Change in Limb	Change in Intestine
0.4 cc 1:100,000	110-128-94	Dilatation	
0.5 cc "	62- 68-53	Dilatation	Constriction
0.7 cc "	72- 80-61	Dilatation and Constriction	Constriction
0.3 cc 1:20,000	80- 92-66	Constriction	Constriction
1.0 cc "	84-106	Constriction	Constriction
1.0 cc "	28- 26		Dilatation*
2.0 cc "			Dilatation*

*Intestine perfused.

1.0 c.c., and when 2.0 c.c., 1:20,000 adrenalin were injected into the jugular vein. (Table III).

Our experiments thus indicate that the mechanisms for dilatation from adrenalin are found in the ungulates.

CARNIVORA

Cats and dogs were the only Mammals known to possess adrenalin vasodilator mechanisms before this research was undertaken. We were interested in finding out whether all families in this order reacted to adrenalin in the same way. Two other families were therefore investigated, viz.—the *mustelidae* and the *procyonidae*.

Mustelidæ (Putorius)

Study of an old ferret (weight 0.6 kgm.) indicated the presence of the vasodilator mechanisms. This evidence was largely limited to depressor effects of adrenalin, 0.2 c.c., 1:1,000,000 causing a fall of 6 mm. from 152 mm. In one instance dilatation of the limb was obtained.

Procyonidæ (Procyon)

Typical adrenalin vasodilator effects were obtained in the raccoon. A marked fall in blood pressure was produced by small doses. (Fig. 9). Dilatation of

FIG. 9
Fall in blood pressure and constriction of the intestine produced by the injection of 0.2 c.c., 1:100,000 adrenalin. Raccoon (Reduced ⅝.)

the limb sometimes resulted from depressor doses. Constriction (Fig. 9) or constriction and dilatation (Fig. 10) occurred in the intestine depending upon

FIG. 10
Dilatation of the intestine produced by 0.3 c.c., 1:10,000 adrenalin, raccoon. (Reduced $\frac{2}{3}$.)

the amount of adrenalin injected, just as in cats and dogs.

RODENTIA

A reason already given that the cat and the dog have been considered possibly exceptions in their behavior toward adrenalin is the fact that the rabbit does not give the same results. We will show, however, judging from the rat and rabbit that rodents are an exception in their behavior toward adrenalin and that the reaction of the cat and dog is the typical one for most mammals.

Muridæ (Mus)

A fall in blood pressure could not be obtained in the white rat. In an animal weighing 0.23 kgm., 0.05 c.c., 1:100,000 adrenalin caused a pure rise from 69 to 83 mm. Smaller doses such as 0.3 c.c., 1:1,000,000 had no effect.

Leporidæ (Lepus)

We have never obtained evidence of the presence of adrenalin vasodilator mechanisms in the rabbit. At least twelve rabbits have been examined in this

connection. It has always been our experience that whenever a dose of adrenalin is large enough to produce any effect, nothing but a pure rise of blood pressure results.

There might, however, be a differential effect without a fall in blood pressure. In one experiment the coeliac, superior mesenteric, inferior mesenteric and renal arteries were tied (5) without changing the reaction to adrenalin.

The limb reaction was determined in four animals. With small doses a dilatation which appeared to be passive, sometimes occurred. When the amount of adrenalin was increased constriction was produced. (Fig. 11). The presence of active dilatation was

FIG. 11
Constriction of the hind limb of a rabbit (2.4 kgm.) from 0.4 c.c., 1:100,000 adrenalin. (Reduced ⅓.)

then sought in another way. The hind limb of an animal was perfused with Ringer's solution, and adrenalin was injected into the jugular vein. If dilator mechanisms sensitive to adrenalin, exist in the sympathetic and dorsal root ganglia, the limb under these conditions should respond. The injection of even large doses of adrenalin into the jugular vein was without effect. Injection into the perfusion fluid as it entered the iliac artery was also without

effect in one animal, while in a second rabbit the fir- two doses (0.5 c.c. and 0.1 c.c., 1:100,000) caused con striction, but later doses had no effect.

In one experiment the sciatic and femoral nerve in one limb had been cut seventeen days before However no evidence of a terminal dilator mechanism could be obtained. In the cat and dog this has been obtained easily by such a method (13, 14).

Very small passive dilatations were produced in the denervated limb of the rabbit when adrenalin was injected into the general circulation. This limb was perfused later, doses of adrenalin varying from 1:1,000,000 to 1:10,000 concentration being injected into the fluid, but without result.

The reaction of the intestine was observed in four animals. In one, there was small passive dilatation with small doses. The other three constricted with doses of this size. In all there was prolonged constriction with large doses (Fig. 12). As an illustra-

FIG. 12
Constriction of the intestine of a rabbit due to the injection of 0.5 c.c., 1:10,000 adrenalin. (Reduced ⅔.)

tion of the amount of constriction; a loop 37 c.c. in volume constricted .72 c.c. after the injection of 0.5 c.c., 1:10,000 into the general circulation.

In an unpublished research we have found that there is a dilator mechanism for the kidney located in the aortico-renal ganglion. One of the methods employed has been to apply adrenalin solutions to the ganglion, noting the volume change in the kidney. We did this in a rabbit, but obtained constriction in the kidney instead of dilatation.

We conclude from our results that rodents do not possess adrenalin vasodilator mechanisms.

PRIMATES

Monkey (Pithecus)

Adrenalin vasodilator mechanisms are present in the monkey (Table IV). Excellent dilatations of a

TABLE IV.

RESPONSE OF THE MONKEY TO ADRENALIN

Dose	Blood pressure change in mm. of Mercury	Limb	Intestine
0.1 cc 1:100,000	90-101-92	Dilatation	Constriction and slight dilatation
0.4 " "	94- 98-86	Dilatation	
1.0 " "	80- 96	Very marked dilatation	
0.3 " 1:10,000	86-124	Marked dilatation	Marked constriction and dilatation
1.3 " "	64-166	Marked dilatation	Marked constriction and dilatation
2.5 " "	64-177	Marked dilatation and constriction	Marked constriction and dilatation

leg were produced (Figs. 14 and 15) by doses of adrenalin ranging from 0.4 c.c., 1:100,000 to 0.7 c.c., 1:10,000 (weight of animal 5.2 kgm.) (The foot was not included in the plethysmograph). Indeed, a large dose of adrenalin was required to cause reversal in the limb (Fig. 16). By perfusing the limb and injecting adrenalin into the jugular vein we attempted to bring the gangliar mechanism into action, without

result. We thought this might be due to failure
the adrenalin to reach the ganglia on account

FIG. 13

Fall in blood pressure in the monkey
1,000,000 adrenalin. (Reduced)

FIG. 14

Response to 0.5 c.c. 1,000,000 adrenalin in the monkey. Constriction followed by dilatation of the intestine. Marked dilatation of the limb. (Reduced ¾.)

clamping the aorta too high up, as that has frequent
been the case in cats. On the other hand injection
the hormone into the perfusion fluid easily produc
dilatation. The explanation, therefore, might be th
the vasodilator myoneural junction and not the ga

glar mechanism was the source of the dilatation. We are inclined to doubt this as being typical, for there is no reason to believe that the monkey is different from the cat and dog in which the ganglionic mechanism is an important source of adrenalin vasodilatation (13).

The intestinal mechanism in the monkey worked

FIG. 15
Effect of a larger dose of adrenalin, 0.3 c.c., 1:10,000 in the monkey. (Reduced ⅔.)

FIG. 16
Reversal in the limb produced by a large dose of adrenalin, 2.5 c.c., 1:10,000 in the monkey. (Reduced ⅔.)

very well (Figs. 14 and 15) until large doses of adrenalin were used when constriction only was obtained (Fig. 16).

A fall in blood pressure was obtained from the injection of small doses of adrenalin (Fig. 13), but as sometimes happens in cats or dogs the fall became small or almost disappeared after a few doses had been injected (Fig. 14).

DISCUSSION

So far as we know the blood vessels of all vertebrates lower than mammals are constricted by adrenalin.

In the frog Burket (17) found that the constrictor effect of succeeding doses of adrenalin rapidly declines until there remains only a very small response. He also noted that the rise in pressure lasts much longer than in the cat. Our observations upon the turtle are somewhat similar, there being a rapid loss in sensitiveness to adrenalin and a prolonged effect when the rise is produced. In addition attention should be called to the fact that the threshold for a blood pressure response is much higher in the reptiles than in the mammals.

It is of interest to note also that birds resemble mammals in some respects in their behavior toward adrenalin. The threshold for adrenalin response is about as low and successive doses of adrenalin do not readily decrease the sensitiveness. The percentage rise in blood pressure that can be produced by adrenalin in the fowl is much greater than that possible in the reptile, although the rise in blood pressure is more prolonged in the fowl than in the mammal. It may be partly due to the absence of dilator mechanisms which could be affected by adrenalin and thus

tend to offset the constrictor effect. Dale (22) was able partially to paralyze the constrictor mechanism in the fowl, but he obtained no fall in blood pressure from adrenalin.

Besides the carnivores and rodents which have been extensively studied by different investigators, a few observations have been made upon the ungulates and primates. Barger and Dale (18) paralyzed the vaso-constrictor mechanism in the pig and the goat with ergotox. but failed to obtain a fall in blood pressure wh adrenalin was injected. Barbour and Prince (19), in experiments with perfused hearts obtained dilatation of coronary vessels in the ox, sheep, pig, and rabbit, but constriction in the monkey.

Auer and Meltzer (20) obtained usu v a rise, but sometimes also a fall in blood pressu the intraspinal injection of large amounts of a in the monkey.

We have been able to show in all orders of mammals which we have studied, except the rodents, that both adrenalin vasodilator mechanisms (for skeletal muscle and intestine) are present. On the other hand, we have been unable to prove the presence of such mechanisms in the rodents. Moreover, no one else (21, 23) has ever been able to produce a fall in blood pressure by the injection of adrenalin in the rabbit. Dale (22) was unable to obtain a reversal by the use of ergot, although he abolished the pressor effect of adrenalin.

Dilatation from adrenalin had been observed in the rabbit. The Meltzers (24) obtained dilatation of the ear vessels of the rabbit from the subcutaneous injection of adrenalin. Ogawa (25) produced dilatation

of the perfused kidney, intestine and hind limbs of the rabbit by adrenalin. However, he usually obtained constriction of the kidney even with dilute solutions. He did not secure a primary dilatation in the limb. We are led to conclude as a result of our experiments that even though adrenalin vasodilatation may occur in the rabbit it is relatively unimportant.

In conclusion, we are justified in assuming that the usual vasomotor reaction in skeletal muscle is dilatation with moderate doses of adrenalin, rodents being exceptional; and because of the uniform occurrence in other mammalian orders as well as the presence in the monkey we have considerable reason for believing that these mechanisms are also present in man.

We wish to thank Lois McPhedran Fraser for assistance in a part of this research

SUMMARY

1. Birds and reptiles possess no adrenalin vasodilator mechanisms.
2. A small amount of adrenalin produces a fall in blood pressure in marsupials, ungulates, carnivores and primates.
3. Adrenalin vasodilator mechanisms for the limb and intestine are present in marsupials, ungulates, carnivores and primates.
4. Rodents are exceptional in their reaction to adrenalin, vasodilator mechanisms sensitive to this hormone being absent.
5. Dilatation in the blood vessels of skeletal muscle is the usual response to adrenalin in mammals.

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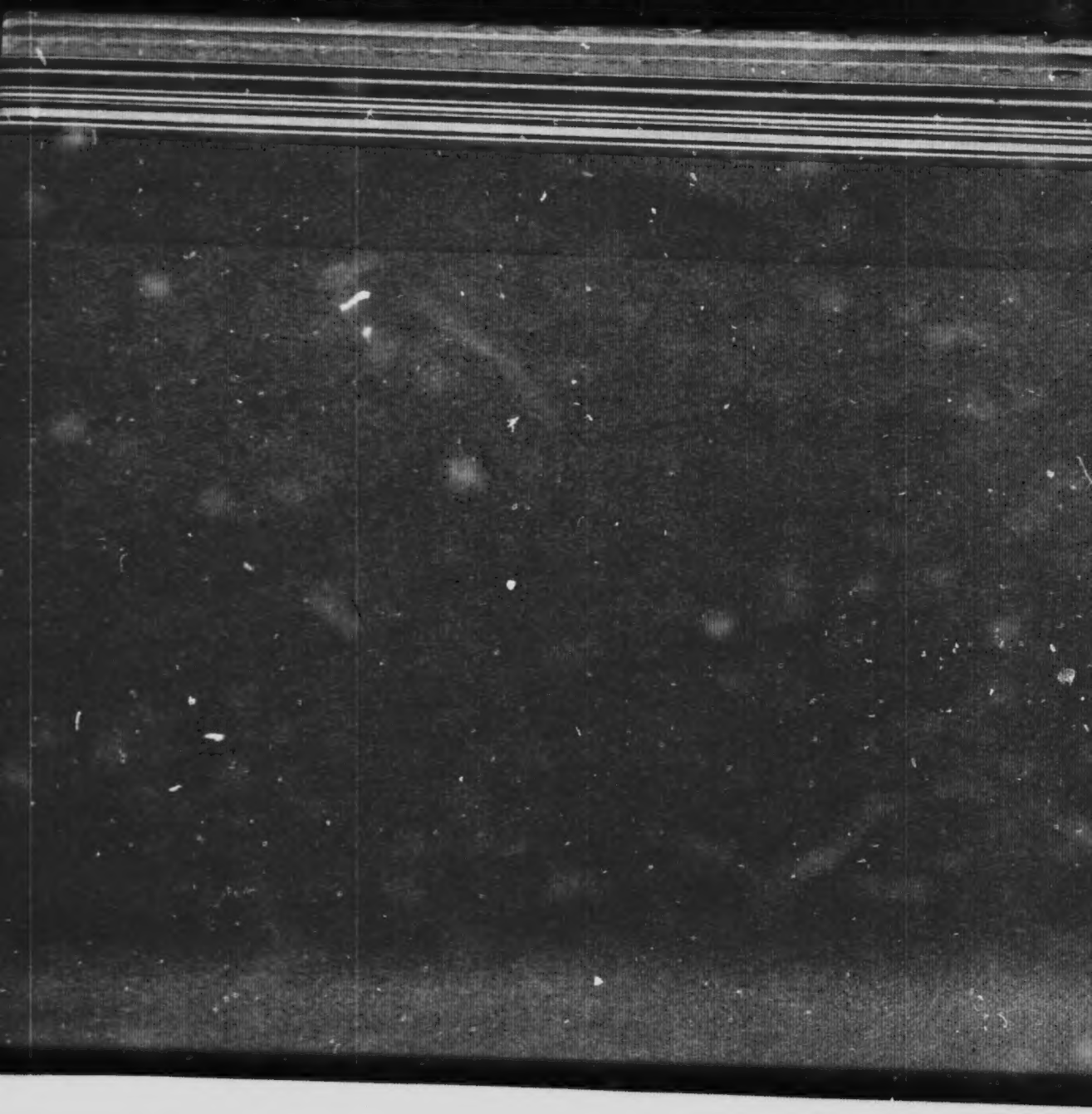

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